

## **REMARKS/ARGUMENTS**

### **Status of the claims**

After entry of this amendment, claims 1 and 16-24 are pending. Claims 1 has been amended. Support for the amendment to claim 1 is found in the specification and claims as originally filed (*see, e.g.*, page 10, lines 5-7). Thus, no new matter is added by these amendments.

### **Restriction requirement**

Applicants acknowledge the Examiner's decision to make the restriction requirement final. Applicants expressly reserve the right under 35 U.S.C. § 121 to file a divisional application directed to the nonelected subject matter during the pendency of this application or an application claiming priority from this application.

### **Claim rejections under 35 U.S.C. § 102**

1. Claims 1 and 16-24 stand rejected under 102(c) as being allegedly anticipated by U.S. Patent No. 5,604,113 to White *et al.* ("White"). To the extent that this rejection applies to the amended claims, Applicants respectfully traverse.

The Examiner has maintained this rejection from the previous Office Action. In maintaining this rejection, the Examiner has not accepted the Applicants' argument that White does not expressly or inherently teach or suggest p53 binding to helicases, and thus, helicase-dependent apoptosis by p53. Specifically, the Examiner alleges that helicase dependent p53-mediated apoptosis is an inherent feature of the teachings of White, stating:

"[S]ince White *et al.* disclose p53-mediated apoptosis, which Applicants do not argue, the reference discloses the basis of the inherency, since the mechanism of p53 apoptosis would be the same. It is the premise of the rejection that only one mechanism is involved in p53-mediated apoptosis. Since the reference discloses determination if the test compound modulates p53-mediate apoptosis, the reference meets the limitation of the claims and inherently meets the limitation of XPB and XPD helicase activity. Applicants can overcome this rejection by showing that the art recognized other mechanisms that mediate p53 apoptosis. *See* Office Action at page 4.

**A.** As a preliminary matter, Applicants respectfully submit again that because White is absolutely silent as to existence of helicases in cells, and thus, of a helicase-dependent mechanism of p53-mediated apoptosis, there is no way that the teachings of White can be construed to teach or suggest, either explicitly or inherently, the active method step of “detecting whether or not the compound is capable of specifically inhibiting binding of the p53 polypeptide to the helicase”, as claimed. A reference simply cannot teach or suggest a detecting step that is based on a protein in a cell that is unknown. The logical conclusion of the Examiner’s reasoning would lead to the result that White would anticipate any claimed method of identifying modulators of p53 mediated apoptosis, regardless of the novelty of a claimed component of a p53 mechanism of apoptosis.

Accordingly, Applicants respectfully resubmit that White does not disclose each and every element of the presently claimed methods, either expressly or inherently, and thus, the reference does not anticipate the invention. Accordingly, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 102(e).

**B.** Moreover, the Examiner has based the rejection on the premise that only one mechanism is involved in p53 mediated apoptosis. Thus, the Examiner has helpfully indicated that this rejection can be overcome by a showing that the art recognized other mechanisms that mediate p53-dependent apoptosis. *See* Office Action at page 4.

Accordingly, Applicants submit the declaration of Dr. Xin Wei Wang which demonstrates that p53 effects apoptosis in cells via multiple mechanisms. In his declaration, Dr. Wang explains that it is known in the art that p53-mediated apoptosis occurs via both transcription-dependent and transcription-independent mechanisms (see Declaration ¶ 7). The transcription-dependent mechanism entails the ability of p53 to induce the expression of pro-apoptotic genes such as BAX, NOXA, PUMA, BID, CD95, APAF-1, DR5, p53AIP1 via p53 transcriptional transactivation of target genes (see Declaration ¶ 8). Other known transcription-independent apoptotic activities of p53 include the direct extranuclear binding of p53 to Bcl protein family members to effect mitochondrial outer-membrane permeabilization (MOMP) (see Declaration ¶ 8).

Dr. Wang further clarifies that the present application is based upon the inventors' elucidation of an additional mechanism for p53-mediated apoptosis that entails the binding of the XPB and XPD helicases to p53, which results in inhibition of helicase activity (see Declaration ¶ 9). Dr. Wang then describe the results of his subsequent work published in a journal article (Zhou *et al.*, *Cancer Research*, 59: 843-848 (1999); "Zhou") which demonstrates that the helicase-binding mechanism for p53-mediated apoptosis is independent of p53's transcriptional activation of pro-apoptotic genes (see Declaration ¶¶ 10-12). Zhou presents experiments demonstrating that when mutants of p53 which have deletions of the p53 C-terminal domain that encompass the XPB and XPD binding site are tested for p53-mediated apoptotic activity, a loss of apoptosis was observed relative to wild type p53 (see Declaration ¶¶ 10-11). Because these C-terminal deletion mutants retained an intact p53 transcriptional transactivation domain, these p53 mutants were able, nonetheless, to induce the expression of a well known pro-apoptotic gene, *Bax* (see Declaration ¶ 12). Based on the experiments described in Zhou, Dr. Wang concludes that that p53 binding to XPD or XPB helicase and p53 induction of pro-apoptotic genes, such as *Bax*, are distinct mechanisms by which p53 effects apoptosis in cells, and that transcription-dependent p53 induction of pro-apoptotic genes is at least one mechanism of p53 mediated apoptosis that is independent of p53 binding to XPD or XPB helicase (see Declaration ¶¶ 13-14).

Applicants respectfully submit that the declaration of Dr. Wang presents evidence unequivocally demonstrating that the art recognized other mechanisms besides helicase binding to p53 which can induce p53-mediated apoptosis. Accordingly, the showing of multiple mechanisms of p53 mediated apoptosis as requested by the Examiner has been provided, and Applicants respectfully request withdrawal of this ground for rejection.

2. Claims 1, and 16-24 stand rejected under 102(e) as being allegedly anticipated by U.S. Patent No. 5,484,710 to Reed *et al.* ("Reed"). To the extent that this rejection applies to the amended claims, Applicants respectfully traverse.

The Examiner has also maintained this rejection from the previous Office Action. In maintaining this rejection, the Examiner has again not accepted the Applicants' argument that

Reed does not expressly or inherently teach or suggest p53 binding to helicases, and thus, helicase-dependent apoptosis by p53.

The substance of the Examiner's rejection based on Reed is the same as for White. Thus, Applicants arguments above with respect to White apply equally to the rejection based on Reed.

Accordingly, Applicants respectfully resubmit that Reed, like White, does not teach or suggest the active method step of "detecting whether or not the compound is capable of specifically inhibiting binding of the p53 polypeptide to the helicase", as claimed. Because Reed does not disclose each and every element of the presently claimed methods, either expressly or inherently, this reference does not anticipate the invention. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 102(e).

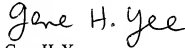
With respect to Reed, the Examiner has used the same premise of a single mechanism of p53 mediated apoptosis in rejecting the present claims as anticipated by inherency. The Examiner has also stated that the rejection based on Reed can be overcome by a showing that the art recognized other mechanisms that mediate apoptosis by p53. Thus, the remarks above and the Declaration of Dr. Wang, which demonstrates that the art recognized multiple mechanisms of p53 mediated apoptosis, and that helicase binding to p53 is only one such mechanism, are equally applicable to overcome the rejection based on Reed. Accordingly, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 102(e).

**CONCLUSION**

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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